Improvement in Blood Pressure, Arterial Stiffness and Wave Reflections With a Very-Low-Dose Perindopril/Indapamide Combination in Hypertensive Patient

A Comparison With Atenolol

Roland G. Asmar, Gérard M. London, Michael E. O'Rourke, Michel E. Safar,
for the REASON Project coordinators and investigators*

Abstract—International guidelines recommend that antihypertensive drug therapy should normalize not only diastolic (DBP) but also systolic blood pressure (SBP). Therapeutic trials based on cardiovascular mortality have recently shown that SBP reduction requires normalization of both large artery stiffness and wave reflections. The aim of the present study was to compare the antihypertensive effects of the very-low-dose combination indapamide (0.625 mg) and perindopril (2 mg) (Per/Ind) with the β-blocking agent atenolol (50 mg) to determine whether Per/Ind decreases SBP and pulse pressure (PP) more than does atenolol and, if so, whether this decrease is predominantly due to reduction of aortic pulse wave velocity (PWV) (automatic measurements) and reduction of wave reflections (pulse wave analysis, applanation tonometry). In a double-blind randomized study, 471 patients with essential hypertension were followed for 12 months. For the same DBP reduction, Per/Ind decreased brachial SBP (−6.02 mm Hg; 95% confidence interval, −8.90 to −3.14) and PP (−5.57; 95% confidence interval, −7.70 to −3.44) significantly more than did atenolol. This difference was significantly more pronounced for the carotid artery than for the brachial artery. Whereas the 2 antihypertensive agents decreased PWV to a similar degree, only Per/Ind significantly attenuated carotid wave reflections, resulting in a selective decrease in SBP and PP. The very-low-dose combination Per/Ind normalizes SBP, PP, and arterial function to a significantly larger extent than does atenolol, a hemodynamic profile that is known to improve survival in hypertensive populations with high cardiovascular risk. (***Hypertension*. 2001;38:922-926.**)

Key Words: antihypertensive therapy ■ pulse wave velocity ■ pulse pressure

Recent epidemiological studies and recommendations of hypertension guidelines[1–3] have directed attention to systolic blood pressure (SBP) as a better guide than DBP for evaluating cardiovascular risk. It has been shown that drug therapy of hypertension frequently results in an adequate control of DBP (≤90 mm Hg), whereas the ability to control SBP (≤140 mm Hg) is achieved less often.[4,5] Such results have focused attention on hemodynamic factors, such as large artery stiffness and wave reflections, which are important determinants of SBP and pulse pressure (PP) and are strong independent cardiovascular risk predictors in hypertensive populations. Consequently, the role of drugs or regimens that may selectively reduce SBP and PP assumes importance.

Very-low-dose combinations involving an ACE inhibitor (ACEI) and a diuretic (D) may be suitable for reducing SBP and PP and, at the same time, for facilitating the compliance with long-term drug treatment.[2,3,6–8] In genetic models of hypertension in rats, the ACEI + D combination was shown to induce a significantly more pronounced pressure-independent decrease in arterial stiffness and reduction of aortic collagen accumulation than that of each component given alone.[9,10] In middle-aged patients with hypertension, although D induces only minor changes in large artery diameter and stiffness, ACEIs and, mostly, the D+ACEI combination are able to normalize arterial stiffness and wall thickness.[10] Thus, it is relevant to evaluate whether a fixed ACEI+D combination is a suitable therapy for selectively reducing SBP and PP by improving arterial stiffness.

The very-low-dose combination Per/Ind combines the diuretic compound indapamide, given at subtherapeutic dosage (0.625 mg per day), with the ACEI perindopril, given at a subtherapeutic dosage (2 mg per day).[6,11] The aim of the present study was to establish whether Per/Ind decreased SBP and PP more than the β-blocking agent atenolol for the same DBP reduction, and whether any such effect was mediated by a Per/Ind-induced decrease in large artery stiffness and attenuation of wave reflections.

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From Hôpital Broussais (M.E.S.), Paris, France; Institut Cardiovasculaire (R.G.A.), Paris, France; Hôpital Manhès (G.M.L.), Fleury-Mérogis, France; and St-Vincent Hospital (M.O.R.), Darlinghurst, Australia.

Correspondence to Prof Michel Safar, Médecine Interne 1, Groupe Hospitalier Broussais–George Pompidou, 96, rue Didot, 75674,Paris Cedex 14 France. E-mail michel.safar@brs.ap-hop-paris.fr

*Please see Appendix for complete list of study coordinators and investigators.

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Methods

The REASON Project (Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind Study) is a multicenter, controlled, randomized, double-blind, 2-parallel groups study conducted in 13 countries (see Appendix). Five hundred sixty-two hypertensive patients, age 18 to 84 years, were preincluded. The inclusion criteria were an essential hypertension defined as a supine SBP ≥160 mm Hg and <210 mm Hg, and/or a supine DBP ≥95 mm Hg and <110 mm Hg. In all cases, hypertension was uncomplicated, and the presence of antidiabetic, hypocholesterolemic, or cardiovascular drug intake was excluded.[7,11] Baseline plasma potassium, creatinine, uric acid, glucose, total cholesterol, and hepatic enzymes were within the normal range. Written informed consent was obtained from each patient, and the protocol was approved by the ethics committees of the individual institutions of the study investigators.

Following the washout placebo period, the patients entered a 12-month double-blind active treatment period and were randomly allocated to either Per (2 mg)/Ind (0.625 mg) or atenolol (50 mg). In both groups, the medication was taken orally in the morning as a single dose. The dosage was then adapted to the blood pressure, and the dose was doubled (2 capsules once daily) after 3 months if SBP remained >160 mm Hg and/or DBP >90 mm Hg. At the end of the procedure, drug dosage was progressively decreased over 8 to 15 days to avoid any complication caused by atenolol.

Hemodynamic investigations were performed 24 hours after the last drug intake, just before inclusion (M0), and at the end of the follow-up period (M12). Each patient was investigated in the morning in a controlled environment of 22±2°C (±1 SD). After a 10-minute rest in the supine position, SBP, DBP, and heart rate were determined using a mercury sphygmomanometer. Arterial measurements were then performed, involving pulse wave analysis (carotid artery, n=124; aorta, n=130) and velocity (n=406). All measurements were analyzed by 2 physicians blinded to treatment, clinical data, and physical examination. Aortic pulse wave velocity (PWV) was determined by an automatic device, the Complior (Colson, Paris), which allows online pulse wave recording and automatic calculation of PWV as previously described and validated.[12] For upper-limb pulse pressure determinations, brachial and radial artery SBP and DBP and mean blood pressures (MBP) were considered equivalent, taking into account the small degree of pressure wave amplification between these 2 sites.[13–16] The carotid pressure wave was measured by applanation tonometry and calibrated from the radial pressure wave, assuming that the mean pressure (determined from integration of the digitized radial wave) was the same at both sites and that brachial and carotid DBP were nearly equal.[13–16] The repeatability coefficients after 1- and 3-month intervals have been previously published.[13–16] The carotid augmentation index (AI), which evaluates the delay of backward wave reflections and its effect on the height of SBP, was determined according to previously validated methods.[13] Aortic blood pressure and augmentation index were measured by pulse wave analysis using an already validated transfer function.[13–16] The degree of PP amplification (PP ampl) was calculated as brachial PP/carotid PP or as brachial PP/aortic PP.

Because differences in large artery function were expected between the 2 groups, aortic PWV was the parameter used to determine the number of subjects. For an expected difference of 0.5±1.2 m/sec, an α-risk of 5%, and a β-risk of 5%, the number of subjects to be analyzed was 300. Data are expressed as mean±SD and analyzed according to a per Protocol evaluation. The comparability of the groups at baseline was assessed by Student's t test for continuous parameters and a χ^2 test for categorical variables. In each group, baseline evaluation and last evaluation were compared by a 2-tailed Student's test for paired samples. Between-treatment comparison of variations of parameter was adjusted for age, gender, and baseline value and performed using ANCOVA. For aortic PWV, MBP, and heart rate (baseline and variation) were also included. Statistical analysis was done by SAS software. A P value ≤0.05 was considered significant.

Results

Among the 471 randomized patients analyzed for safety, 406 (86%) were analyzed in the efficacy per protocol population (Per/Ind, 204; atenolol, 202). In baseline conditions, the 2 populations did not differ in terms of age, gender, and body mass index. During the follow-up, 184 subjects in the Per/Ind group and 170 subjects in the atenolol group completed the active treatment period (12 months).Ninety-six patients in the randomized population withdrew (Per/Ind, 44; atenolol, 52). The frequency of withdrawal was significantly higher for atenolol in terms of lack of efficacy (Per/Ind, 10; atenolol, 24) and was the same for Per/Ind and atenolol for adverse events (respectively, 19 and 20 patients) and major protocol deviation (respectively, 3 and 2). There were 12 withdrawals because of nonmedical reasons in the Per/Ind group and 6 in the atenolol group.

Regarding brachial blood pressure (Table 1 upper panel), the decreases in SBP, PP, and MBP were significantly higher with Per/Ind than with atenolol. For SBP and PP, the adjusted between-group differences were, respectively, −6.02 (95% confidence interval [CI], −8.90 to −3.14) and −5.57 (95% CI, −7.70 to −3.44) (P<0.001). The decrease in brachial DBP was significant in each treatment group, but there was no difference between the two groups (P=0.715). Heart rate was significantly reduced in the atenolol group (P<0.001). The PWV decreased significantly in each treatment group (P<0.001) and almost identically (P=0.258) with the 2 drugs. The same results were obtained after adjustment on MBP and heart rate baseline and changes.

In the pulse wave analysis population (Table 1 lower panel), the carotid and aortic SBP and PP decreased significantly in the two groups. There was no difference in the baseline values of this population compared with the total population. These decreases were substantially higher with Per/Ind than with atenolol, and adjusted between-group differences were highly significant (P<0.001). The carotid and aortic AI and PP amplification were, respectively, significantly lower and higher with Per/Ind compared with atenolol. With Per/Ind, the AI decreased. The decrease was significant at the aortic (P=0.002) but not the carotid level (within-group comparison). The AI decrease on Per/Ind contrasted with the increase on atenolol with a significant difference between the 2 groups (P=0.036 for the carotid AI; P<0.001 for the aortic AI). The significance disappeared after adjustment to heart rate.

There were 96 emergent adverse events in 60 patients given atenolol and 94 events in 66 patients receiving Per/Ind. The most frequently related adverse events (≤5%) were headache, dizziness, asthenia, and cough. There were 39 dropouts because of adverse events: Per/Ind, n=19 (8.1%); and atenolol, n=20 (8.5%). Serum potassium was <3.4 mmol/L in 7 patients (3.0%) on Per/Ind and in 3 patients (1.3%) on atenolol (P=NS) (Table 2).

Discussion

In this study, we compared the antihypertensive effects of the low-dose combination Per/Ind with the standard antihypertensive agent atenolol. After 1-year follow-up, the brachial SBP, DBP, MBP, and PP had decreased significantly in the 2 treatment groups. The decrease in DBP was the same in each treatment group, whereas the Per/Ind combination had a more marked effect on brachial SBP, PP, and MBP and reduced them significantly more than did atenolol. Similar differences have been previously described with nitrates[17,18] but not with the usual standard antihypertensive agents.[13,19] In a previous double-blind study comparing the

TABLE 1. Changes in Brachial, Carotid, and Aortic Blood Pressure; Heart Rate; and Carotid-Femoral PWV in the Per/Ind and Atenolol Groups

Parameters	Per/Ind	Atenolol	Adjusted Between-Group Difference* (95% CI)	*P* Value†
Brachial SBP, mm Hg				
Baseline	163.3±13.6	161.0±14.1		
Change from baseline	−23.1±15.6‖	−16.2±16.0‖	−6.02 (−8.90 to −3.14)	<0.001
Brachial DBP, mm Hg				
Baseline	98.8±7.0	98.6±6.9		
Change from baseline	−13.3±8.6‖	−12.9±9.6‖	−0.32 (−2.01 to 1.38)	0.715
Brachial MBP, mm Hg				
Baseline	120.3±6.6	119.4±6.6		
Change from baseline	−16.6±9.8‖	−14.0±10.3‖	−2.29 (−4.20 to −0.38)	0.019
Brachial PP, mm Hg				
Baseline	64.5±15.1	62.3±15.7		
Change from baseline	−9.9±12.4‖	−3.3±13.5‖	−5.57 (−7.70 to −3.44)	<0.001
Heart rate, bpm				
Baseline	72.4±9.8	72.3±9.1		
Change from baseline	−1.4±9.2‡	−7.8±9.7‖	6.45 (4.86 to 8.04)	<0.001
PWV, m/sec				
Baseline	12.28±2.94	12.27±2.79		
Change from baseline	−0.79±1.91‖	−0.99±2.05‖	0.19 (−0.14 to 0.53)	0.258
Carotid SBP, mm Hg				
Baseline	154.6±17.5	151.3±16.0		
Change from baseline	−23.2±17.2‖	−7.2±15.0‖	−14.37 (−19.69 to −9.04)	<0.001
Carotid PP, mm Hg				
Baseline	58.8±18.5	53.7±15.1		
Change from baseline	−12.9±13.9‖	3.4±12.5‡	−13.88 (−18.18 to −9.59)	<0.001
Carotid AI, %				
Baseline	27.9±18.5	27.5±21.5		
Change from baseline	−3.1±17.5¶	2.7±15.6¶	−5.57 (−10.77 to −0.36)	0.036
PP amplification (ratio)				
Baseline	1.16±0.23	1.22±0.23		
Change from baseline	0.03±0.28¶	−0.13±0.23‖	0.12 (0.05 to 0.19)	<0.001
Aortic SBP, mm Hg				
Baseline	155.2±17.1	150.7±17.1		
Change from baseline	−22.5±17.0‖	−8.0±16.6‖	−12.52 (−17.97 to −7.08)	<0.001
Aortic PP, mm Hg				
Baseline	56.3±17.7	53.4±16.5		
Change from baseline	−9.3±11.7‖	2.3±12.0¶	−10.34 (−14.12 to −6.56)	<0.001
Aortic AI, %				
Baseline	29.4±10.1	30.1±10.0		
Change from baseline	−3.1±7.7§	1.8±9.1¶	−5.17 (−7.74 to −2.61)	<0.001
PP amplification (ratio)				
Baseline	1.27±0.23	1.27±0.21		
Change from baseline	−0.03±0.26¶	−0.11±0.22‖	0.07 (0.01 to 0.14)	0.021

Values are mean±SD.

For brachial and PWV measurements, the number of subjects was, respectively, 204 and 202. For the central measurements, the number of subjects was 65 and 64.

*Difference adjusted for age, gender, and baseline value.

†Fisher test of ANCOVA.

‡$P<0.05$, §$P<0.01$, ‖$P<0.001$, ¶P=NS.

TABLE 2. Variation in Biochemistry Parameters (mmol/L) During the Follow-Up

Value, mmol/L	Per/Ind (n=232)	Atenolol (n=225)	*P* Value*
Sodium	−1.3±2.8	−1.1±2.8	0.355
Potassium	−0.16±0.44	0.00±0.45	<0.001
Uric acid	46.9±63.6	32.2±43.6	0.004
Creatinine	4.0±9.7	1.7±7.7	0.005
Glucose	0.05±0.7	0.10±0.7	0.487
Triglycerides	−0.01±0.71	0.22±1.32	0.023
Total Cholesterol	0.03±0.75	0.10±1.04	0.397
HDL Cholesterol	0.07±0.24	−0.00±0.25	0.002
LDL Cholesterol	−0.01±0.73	−0.02±0.65	0.846

Values are mean±SD.

Per/Ind (n=218), atenolol (n=218) for triglycerides and total cholesterol (total cholesterol); Per/Ind (n=217), atenolol (n=216) for chloride; Per/Ind (n=214), atenolol (n=218) for glucose; Per/Ind (n=233), atenolol (n=226) for creatinine; Per/Ind (n=210), atenolol (n=209) for HDL; Per/Ind (n=182), atenolol (n=177) for LDL.

**P* Value: Student's *t* test.

ACEI fosinopril given alone to atenolol, Chen et al[20] did not find any between-group difference in terms of changes in either SBP or PP. Thus in the present study, it is the combination of the low-dose ACEI perindopril with low doses of D, which was probably responsible for the greater decrease in SBP and PP obtained with Per/Ind compared with atenolol.

The decrease in carotid and aortic blood pressures was significantly more pronounced with the Per/Ind combination than with atenolol. The blood pressure effect profile clearly differed between Per/Ind, which induced a similar effect on central (carotid and aortic) and peripheral (brachial) blood pressures, and atenolol, which has an even smaller central than peripheral effect. This findings is important to consider because several epidemiological studies have recently shown that SBP and PP are the most relevant mechanical factors for predicting cardiovascular risk.[21] Furthermore, it has been shown that a reduction of PP amplification also is considered to be a significant independent cardiovascular risk factor.[22] Thus, it is important to note in this study that Per/Ind contributed more to maintaining PP amplification than did atenolol. Another important result from this investigation was that with Per/Ind, nearly-normal values of brachial SBP and PP could be achieved in the presence of even lower values of carotid and aortic SBP and PP, as previously observed with other antihypertensive agents such as nitrates or the ACEI perindopril.[15,17] This finding suggests, in contrast to other published data,[23] that the antihypertensive effects of ACEI may be observed only at the site of central arteries, whereas brachial blood pressure itself appears to remain within the normal range.

Three hemodynamic factors could explain that central blood pressure decreased more with Per/Ind than with atenolol: alterations in ventricular ejection time, reduction of aortic PWV, and modification of the reflectance (changes in the site or intensity of wave reflections).[13] The reduction of heart rate and the longer ventricular ejection time produced by the β-blocking agent may have delayed the peak of the forward wave, thus inducing an AI increase and contributing to the carotid AI differences between atenolol and Per/Ind.[13] As shown in Results, the role of this factor could not be minimized. On the opposite, a major role of the second factor (represented by the aortic PWV reduction) can be excluded because the PWV changes were identical with Per/Ind and atenolol. The role of the third factor is suggested by the significant decrease in aortic AI under Per/Ind and can result from more distant reflecting sites and/or changes in the reflective properties of these sites.[13,15] Reflection sites are physiologically located at the origin of resistant arterioles, ie, very close to the distal muscular conduit arteries. Because in these particular territories, the wall/lumen ratio of muscular arteries and arterioles has been shown to be markedly reduced by ACEI or the Per/Ind combination but not by atenolol after long-term treatment,[10,24,25] the contrasting changes in vascular structure and/or function between Per/Ind and atenolol might be an explanation for differential patterns of wave reflections, with a more substantial reduction of SBP and PP on Per/Ind than atenolol. Studies in elderly hypertensive subjects have also shown that the wall/lumen ratio of arterioles is positively associated with PP.[26]

Therapeutic trials in populations at high cardiovascular risk have recently shown that the pharmacological treatment of hypertension is associated with a longer survival when the reduction in BP is associated with a significant improvement in large artery function in terms of PWV and wave reflections.[27] Independently of the role of these 2 mechanical factors, it has been shown that survival is also influenced by the presence of a drug treatment involving ACEI and salt and water depletion irrespective of the presence of any other antihypertensive agent.[27] In the present study, Per/Ind reduced selectively SBP and PP in association with significant changes in large artery function, involving a decrease in aortic stiffness and mostly an attenuation of wave reflections. Because the results were observed in subjects with relatively mild forms of hypertension, it remains to be seen whether, in the most common forms of human hypertension, Per/Ind is able to reduce cardiovascular risk significantly through its action on large artery stiffness and wave reflections.

Appendix

Coordinators are marked with an asterick (*).

France—M.E. Safar, Paris; R. Asmar, Paris; J.M. Mallion*, Grenoble; P.H. Baguet, Grenoble; M. Andrejak, Amiens; B. Chamontin, Toulouse; J. Amar, Toulouse; T. Brillac, Toulouse; P. Fressinaud, Angers; G. Berrut, Angers; J. Daugy, Angers; P. Gosse, Bordeaux; V. Jullien, Bordeaux; D. Herpin, Poitiers; S. Ragot, Poitiers; B. Levy, Paris; G. London, Ste Geneviève des Bois; A. Guerin, Ste Geneviève des Bois; S. Marchais, Ste Geneviève des Bois; B. Pannier, Ste Geneviève des Bois; R. Luccioni, Marseille; P. Ambrosi, Marseille; H. Michalski, Perpignan; O. Gourdon, Perpignan; C. Tardy, Perpignan; C. Delhomme, Montpellier; A. Mimran, Montpellier; G.D.U. Cailar, Montpellier; S. N'guyen, Montpellier; D. Stephan, Strasbourg; P. Desarnauts, Strasbourg; A. Zech, Strasbourg; J.L. Imbs, Strasbourg; C. Thuillez, Rouen; R. Joannides, Rouen; M. Godin, Rouen; B. Vaisse, Marseille; J.L. Poggi, Marseille; F. Silhol, Marseille; Y. Weiss, Meaux; F. Tertrain, Meaux; J.M. De Kermadec, Meaux; C. Cavat, Domène; B. Chassery, Fontaine; P. Jallon, Meylan; J.M. Senechal, Grenoble; J.P. Bondois, Amiens; C. Boulnois, Cagny; A. Delannoy, Moreuil; P. Desobry, Warloy Baillon; M. Bonnefoy, Seysses; J.P. Boyes, Seysses; T. Brillac, Toulouse; B. Dauptain, Pamiers; M. Hercyk, Gragnague; P. Monsegur, Toulouse; L. Rouperas, Launac; P. Igigabel, Tierce; M. Lambert, Angers; A. Mario, Angers; J. Tondut, Angers; R.

Gaudichon, Angers; M. Quenelle, Avrille; J.P. Hubault, Avrille; B. Courtot, Carbon Blanc; P. Dejean, Bordeaux; F. Devenyns, Bordeaux; J. Gayet, Bordeaux; P. Guerin, Bordeaux; F. Paccalin, Bordeaux; P. Uge, Bordeaux; X. Magnac, Beglas; M. Behar, Long Pont sur Orge; R. Benady, Marcoussis; J. Cimignani, Athis Mons; J. Rebot, Epinay sur orge; P. Beffara, Bages; D. Ching, Leucate; G. Elgrishi, Leucate; J.L. Englebert, Perpignan; C. Malzac, Perpignan; R. Said, Perpignan; D. Sar, Fourques; M. Tabary, Le Barcares; J.F. Badina, Strasbourg; T. Geist, Strasbourg; P. Marmor, Strasbourg; B. Adam, Rouen; J. Ennasr, Rouen; P. Mazingue DeSailly, Rouen; G. Pelage, Rouen; D. Bousquet, Marseille; G. Recorbet, Marseille; and M. Vauthier, Marseille.

Australia—M.F. O'Rourke*, Darlinghurst; R. Gordon, Greenslopes; B.M. Grath, Clayton; T. Morgan, West Heidelberg; and R. Zazest, North Adelaide.

Spain—R. Romero*, Badalona; J. Bonet, Badalona; B. Bayés, Badalona; C. Calvo, Santiago de Compostela; E. Lopez Paz, Santiago de Compostela; J. Olivan Martinez, Sevilla; E. Ramos Gonzalez, Sevilla; C. Fernandez Andrade, Sevilla; C. Navarro, Valentina Garcia, Sevilla; A. Roca Cusachs, Barcelona; Teresa Benet, Barcelona; José Luis Palma-Gamiz, Madrid; Alberto Calderón, Madrid; Santos Casado Perez, Madrid; T.A. Rico Zalba, Madrid; B. Marron, Madrid; J.L. Rodicio, Madrid; L. Guerrero, Madrid; M. Cruz Casal, Madrid; and J. Herrera Pérez De Villar, Oviedo.

Germany—K.H. Rahn*, Münster; D. Barenbrock, Münster; R. Kisters, Münster; R.M. Lederle, Dortmund; N. Prokynitopoulos, Nienburg-Langendamm; A. Schreckenberg, Weyhe-Mitte; J. Zehner, Passau; Lehmann, Passau; and R. Krallinger, Fürstenzell.

Italy—B. Trimarco*, Napoli; N. De Luca, Napoli; G. Cerasola, Palermo; G. Mule, Palermo; R. De Cesaris, Foggia; A. Andriani, Foggia; I. Ieva, Foggia; P. Panettieri, Foggia; M. Giardinieri, Roma; F. Ceccarelli, Roma; G. Coliviveti, Roma; L. Nosorti, Roma; E. Uslenghi, Cuneo; and G. Uliengo, Cuneo.

Ireland—D. Fitzgerald* and E. O'Brien.

Sweden—T. Hedner*, Göteborg; B. Polhem, Grästorp; and G. Dahlen, Grästorp.

Belgium—D. Duprez*, Gent; I. Vanhoudt, Gent; P. Debackere, Gent; D. Feys, Gent; L. Delvaux, Gent; P. Cleen, Zwijnaarde; M. Fiers, Mariakerke; E. Schatteman, Dronger; P.G. Silance, Bruxelles; and P. Vandenbossche, Bruxelles.

The Netherlands—P.W. De Leeuw*, Maastricht; F. Kroon, Maastricht; B. Houben, Maastricht; and W. Spiering, Maastricht.

United Kingdom—P. Sever*, London; N. Chapman, London; C.J. Bullpitt, London; S. Bonapace, C. Rajkumar, London; S. Jackson, London; J. Close, London; D. Lyons London; J.L. Reid, Glasgow; and A. Mc Kay, Glasgow.

Austria—G. Hitzenberger*, Wien; D. Magometschnigg, Wien; and F. Skrabal, Graz.

Switzerland—E. Battegay* and K. Tschudin, Basel.

Portugal—J. Polonia*, Porto; J. Maldonado, Porto; J. Alberto Da Silva, Porto; G. Campelo, Porto; J. Gorjao Clara, Lisboa; F. Morais, Lisboa; and G. Silva Nunes, Lisboa.

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